Natural Product Synthesis

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Asymmetric Total Synthesis of Mycoleptodiscin A**

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Abstract: *The first total synthesis of mycoleptodiscin A, a structurally unusual indolosesquiterpenoid possessing an ortho-benzoquinone motif, has been accomplished. A sulfone alkylation coupled two readily available fragments to give an aryl triene intermediate. The tetracyclic core of the molecule was assembled through a highly enantioselective iridium-catalyzed polyene cyclization. The benzylic homologation was achieved by a cationic cyanation. The indole motif was constructed via a copper-mediated intramolecular C–N bond formation at a late stage.*

Indolosesquiterpenoids have recently attracted much attention in the fields of chemical synthesis and biosynthesis .[1–3] Mycoleptodiscins A and B (**1** and **2**, Figure 1) are a pair of indolosesquiterpenoids isolated by Cubilla-Rios et al. from endophytic fungus *Mycoleptodiscus* sp. in 2013.[4] Compound **2** displays significant cytotoxicity against cancer cell lines, while the biological activity of **1** was not reported, which is possibly due to its scarcity from the natural source. From a structural perspective, **1** contains an indole motif linked to the sesquiterpenoid framework at the C4 position, which is relevant to indole terpenoids such as hapalindole H (**3**) and petromindole (**4**).[5,6] Biosynthetically, a Friedel–Crafts reaction may be responsible for the indole C4 alkylation. However, this seemingly straightforward biomimetic transformation proves to be problematic in chemical synthesis, which is due to the lower nucleophilicity at C4 than that at C2. A few elegant alternative strategies have been developed to address the issue, such as reductive Heck annulation[7] and indoline Friedel–Crafts cyclization.[8] In the particular case of **1**, the unusual *ortho*-benzoquinone moiety brings extra difficulties to the execution of these strategies; for instance, for the reductive Heck approach, preparing the 4-Br indole precursor is non-trivial. Thus, the synthesis of **1** could be divided to two problems: 1) assembly of the multisubstituted indole motif;[9] and 2) construction of the sesquiterpenoid framework in an asymmetric fashion. Herein, we describe the first total synthesis of **1** using a highly enantioselective Ir-catalyzed polyene cyclization and a Cu-mediated aryl amination to solve the above problems.

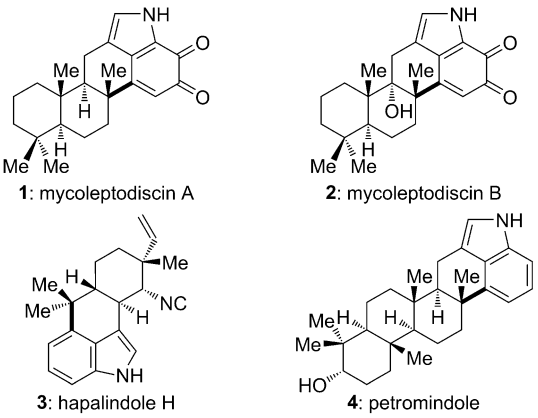
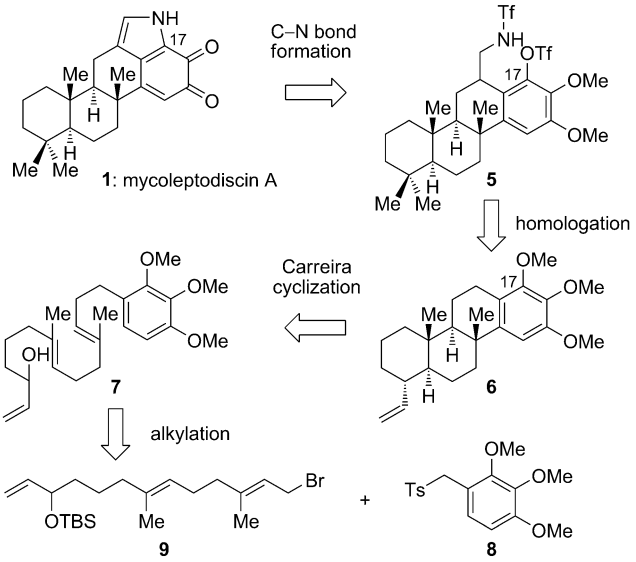


Figure 1. Mycoleptodiscins A and B and related C4-alkylated indole terpenoids.

We undertook a retrosynthetic analysis of **1** (Scheme 1). The *ortho*-benzoquinone moiety could be masked as a catechol dimethyl ether. The indole system was disassembled at the C17–N bond to give an intermediate such as **5**. A transition-metal-mediated aryl amination reaction was envisioned for the ring closure. Compound **5** was further simplified to a tetracycle such as **6**, and a cationic cyanation was anticipated to effect the homologation. The C17



Scheme 1. Retrosynthetic analysis of mycoleptodiscin A.

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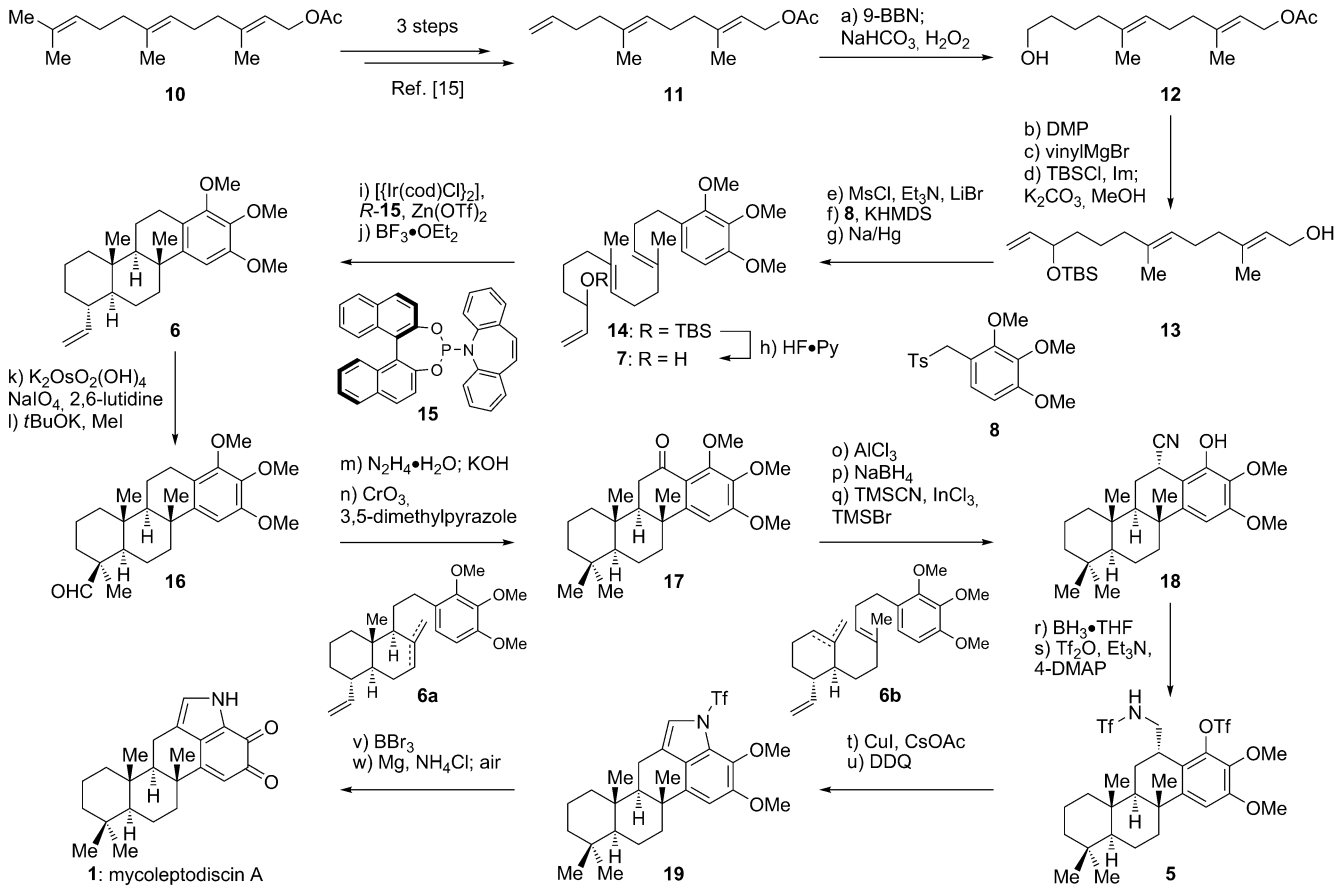
methoxyl could serve as the precursor of a triflate. The enantioselective synthesis of **6** would be a key step. The Carreira cyclization,[10] namely the Ir-catalyzed asymmetric polyene cyclization, has emerged as a powerful method in organic synthesis.[11,12] We recently applied it to the total synthesis of taiwaniadducts.[13] However, in most cases, the reaction was used for assembling bi- and tricyclic systems. Carreira described the only example of tetracycle formation;[10] it would be interesting to showcase such a tandem cyclization in natural product synthesis. We considered aryl triene **7** as a cyclization precursor, and the electron-rich arene may facilitate the final Friedel–Crafts type trapping of the cation intermediate. Compound **7** was traced back to sulfone **8** and bromide **9**, the coupling of which may rely on alkylation and reductive desulfonation.[14] Both **8** and **9** could be readily prepared from commercially available materials.

The synthesis commenced with preparing the polyene **7** (Scheme 2). Farnesyl acetate (**10**) was subjected to a three-step sequence (dihydroxylation, diol cleavage, and methylenation) developed by Schulz et al. to reach terminal olefin **11**.[15] Positional selective hydroboration followed by peroxide cleavage afforded alcohol **12** (86%). Dess–Martin oxidation formed the aldehyde, exposure of which to vinylMgBr gave a secondary allylic alcohol. The alcohol underwent silyl protection and deacetylation to afford primary alcohol **13** with good overall efficiency. Bromination gave compound **9**, which is unstable against moisture and thus needs to be directly subjected to the next alkylation in a crude form.



Scheme 2. Total synthesis of mycoleptodiscin A. Reagents and conditions: a) 9-BBN (1.05 equiv), THF, 22 °C, 24 h, then aq. $NaHCO_3$, aq. H_2O_2 (30 wt%), 0 °C, 2 h, 86%; b) DMP (1.2 equiv), CH_2Cl_2, 22 °C, 1 h, 90%; c) vinylmagnesium bromide (1.05 equiv), THF, −78 °C, 1 h, 87%; d) TBSCl (1.1 equiv), imidazole (1.2 equiv), DMF, 22 °C, 1 h; K_2CO_3 (1.0 equiv), MeOH, 22 °C, 2 h, 98%; e) MsCl (3.0 equiv), Et_3N (5.0 equiv), LiBr (10.0 equiv), THF, −20 °C, 1 h; f) KHMDS (1.05 equiv), THF, −78 °C, 1 h, then **9**, −78 °C, 1 h, 85% (2 steps); g) Na(Hg) (2.0 equiv), Na_2HPO_4 (4.5 equiv), MeOH, −20 °C, 1 h; h) HF·py/THF (1:10), 22 °C, 4 h, 82% (2 steps); i) [{Ir(cod)Cl}$_2$] (4 mol%), *R*-**15** (16 mol%), $Zn(OTf)_2$ (20 mol%), DCE, 22 °C, 16 h, 21% of **6** + 58% of cascade-interruption products; j) $BF_3{\cdot}OEt_2$ (2.5 equiv), CH_2Cl_2, 0 °C, 1 h, 87%; k) $K_2OsO_2(OH)_2$ (10 mol%), 2,6-lutidine (1.0 equiv), $NaIO_4$ (3.0 equiv), acetone/water (3:1), 22 °C, 8 h, 84%; l) *t*BuOK (10 equiv, MeI (10 equiv), *t*BuOH, 3 h, 89%; m) $N_2H_4{\cdot}H_2O$ (10.0 equiv), diethylene glycol, 160 °C, 2 h, then KOH (10.0 equiv), 180 °C, 4 h, 81%; n) 3,5-dimethylpyrazole (20.0 equiv), CrO_3 (20.0 equiv), 0 °C, 1 h, 85%; o) $AlCl_3$ (1.1 equiv), CH_2Cl_2, 22 °C, 2 h, 87%; p) $NaBH_4$ (1.0 equiv), MeOH/CH_2Cl_2 (1:1), 0 °C, 30 min, 92%; q) TMSBr (20 mol%), $InCl_3$ (10 mol%), TMSCN (1.2 equiv), MeCN, 22 °C, 1 h, 89%; r) $BH_3{\cdot}THF$ (2.1 equiv), THF, 50 °C, 3 h; s) Tf_2O (2.1 equiv), Et_3N (3.0 equiv), 4-DMAP (10 mol%), CH_2Cl_2, 0 °C, 30 min, 73% (2 steps); t) CuI (4.0 equiv), CsOAc (10.0 equiv), NMP, 160 °C, 4 h, 64% + 27% of recovered **5**; u) DDQ (5.0 equiv), toluene, 110 °C, 4 h, 71%; v) BBr_3 (10.0 equiv), CH_2Cl_2, −78→22 °C, 15 min, then 22 °C, 30 min; w) Mg (10.0 equiv), NH_4Cl (2.0 equiv), MeOH, sonication, 5 min, then work up under an air atmosphere, 89% (2 steps). cod = 1,5-cyclooctadiene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 4-DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, KHMDS = potassium hexamethyldisilazane, Ms = methanesulfonyl, OTf = triflate, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

Treatment of **9** with the carbanion of sulfone **8** provided the alkylation product in 85% yield, and reductive desulfonation (sodium amalgam) occurred smoothly to furnish compound **14**.[14] In this case, the above route is more efficient and flexible than the previous ones used by Carreira[10] and us[13] for preparing similar polyene precursors (the Suzuki–Miyaura coupling approach, see the Supporting Information for comparison). Desilylation of **14** gave **7** in 82% yield for the two steps.

We then investigated the enantioselective cascade cyclization (Scheme 2). Under the standard conditions (namely [{Ir(cod)Cl}$_2$], ligand *R*-**15**, Zn(OTf)$_2$), the desired product **6** was isolated in 21% yield. A large portion of cascade-interruption products (presumably **6a** and **6b**)[16] were obtained in 58% yield. Exposure of this mixture to $BF_3{\cdot}OEt_2$ gave another portion of **6** (87%), which increased its overall yield to 71% (from **7**). The relative stereochemistry of **6** was determined by X-ray crystallographic analysis[17] (Figure 2), and its enantiopurity was measured to be >99% *ee* by HPLC after further derivatization. The cyclization was reliably performed on gram scale.

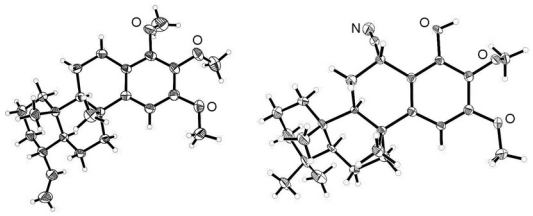


Figure 2. ORTEPs of tetracycle **6** and nitrile **18**.

We functionalized the tetracyclic core (Scheme 2). Although the conversion of the vinyl to the desired *gem*-dimethyl consumes additional efforts, the intermediates along the route provide opportunities for syntheses of analogues with higher oxidation states. Compound **6** underwent a one-pot dihydroxylation/cleavage, and the resultant aldehyde was *C*-methylated by treatment with *t*BuOK and MeI to afford compound **16** as a single diastereomer bearing an axial aldehyde substituent. Wolff–Kishner–Huang reduction (N_2H_4, then KOH, diethylene glycol)[18] followed by benzylic oxidation[19] gave ketone **17** with good overall efficiency. The carbonyl group served as a handle for the homologation process. Demethylation of **17** with $AlCl_3$ followed by $NaBH_4$ reduction provided a mixture of diastereomeric alcohols (ca. 1:1, inconsequential), setting the stage for the homologation.

We examined a variety of conditions for benzylic cyanation (Table 1). Exposure of the benzylic alcohol to $BF_3{\cdot}OEt_2$ and TMSCN gave nitrile **18** in 44% yield (Entry 1), and severe decomposition of the starting material was observed. Lewis acids such as $FeCl_3$, Bi(OTf)$_3$, and Zn(OTf)$_2$ (Entries 2–4) failed to improve the cyanation efficiency. Inspired by the work of Baba and co-workers,[20] we found that $InBr_3$ and $InCl_3$ are more effective promoters (Entries 5 and 6), and MeCN is a superior solvent (Entry 7). Finally, the combination of $InCl_3$ and TMSBr turned out to be optimal,[20b] and **18** was obtained in 89% yield as a single diastereomer. Its

Table 1: Investigation of conditions for benzylic cyanation.

Entry	Conditions[a]	Yield of **18** [%]
1	$BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C	44
2	$FeCl_3$, CH_2Cl_2, 22 °C	57
3	Bi(OTf)$_3$, CH_2Cl_2, 22 °C	46
4	Zn(OTf)$_2$, CH_2Cl_2, 22 °C	52
5	$InBr_3$, CH_2Cl_2, 22 °C	68
6	$InCl_3$, CH_2Cl_2, 22 °C	66
7	$InCl_3$, MeCN, 22 °C	71
8	$InCl_3$, TMSBr (0.2 equiv), MeCN, 22 °C	89

[a] 10 mol% of catalyst, 2.0 equiv of TMSCN.

structure was confirmed by X-ray crystallographic analysis[17] (Figure 2). The cyano group possesses a pseudo-equatorial conformation. Reduction of **18** with $BH_3{\cdot}THF$ gave a primary amine, which was directly subjected to triflating conditions to give compound **5**.[21]

The completion of the synthesis relied on a C–N bond forming reaction. We first examined the conditions of Buchwald–Hartwig amination[22] on the basis of the investigations by Shekhar and co-workers with relevant substrates (sulfonamides and sulfonates).[23] Under their optimized conditions ([Pd$_2$(dba)$_3$], *t*BuXphos, K_3PO_4, *t*AmOH, 80–100 °C), the desired cyclization was not observed. Instead, the release of the free phenol through triflate hydrolysis occurred after prolonged reaction times. We tested ligands (CyXphos, Sphos, BINAP, Xantphos, Josiphos-CyPF*t*Bu), Pd sources (Pd(OAc)$_2$, [{Pd(allyl)Cl}$_2$], $PdCl_2$), solvents (1,4-dioxane, toluene), and inorganic bases (Cs_2CO_3, K_2CO_3) orthogonally, but failed to detect the cyclization product. Although Cu-mediated amination reactions of aryl triflates are rather rare compared with those of halides,[24,25] a procedure (CuI, CsOAc, NMP) modified from that of Fukuyama et al.[26] delivers the indoline in 64% yield along with 27% of recovered **5**. Notably, NMP was a superior solvent to previously reported DMSO[26] (<20% yield) in this case. DDQ oxidation of the indoline gave indole derivative **19** (71%). A sequence of methyl deprotection, reductive desulfonation, and spontaneous aerobic oxidation provided mycoleptodiscin A (**1**) with good overall efficiency. The spectra and physical properties of the synthetic sample are identical with those reported for the natural product, which verifies its absolute configuration.

In summary, we have accomplished the total synthesis of **1**. A scalable asymmetric Ir-catalyzed polyene cyclization was exploited to assemble its core structure. A Cu-mediated aryl amination using a triflate substrate was responsible for the construction of the multisubstituted indole moiety. The chemistry developed may facilitate the biological and biosynthetic studies of the mycoleptodiscin family and find more applications in indole terpenoid synthesis.

Keywords: allylic substitution · C–N bond formation · indole terpenoids · iridium catalysis · polyene cyclization

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[16] These olefin products have essentially same polarities and cannot be separated with the silica gel column, preparative TLC, and HPLC conditions that we tested. Their structures are postulated based on the NMR spectroscopy and MS analyses of the mixture.

[17] CCDC 1045104 (**6**) and 1045105 (**18**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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